

REMARKS

Claims 12-39 and 58-73 are cancelled herein without prejudice or disclaimer and Applicant reserves the right to pursue subject matter of such claims in one or more continuing patent applications. Claims 74-128 are new and find basis in the claims as originally filed and in the specification throughout (e.g., paragraphs 0007, 0024, 0026, 0027, 0030, 0107, 0108 and 0230-0251). Accordingly, no prohibited new matter is introduced by entry of the new claims.

The Office rejected claims in the outstanding action for alleged obviousness, as summarized hereafter:

- i. Claims 12-22, 24, 26-32, 34-39 and 58-73 were rejected under 35 U.S.C. 103(a) over Zabeau (WO00/66771) in view of Little;
- ii. Claims 23 and 33 were rejected under 35 U.S.C. 103(a) over Zabeau and Little in view of McCarthy (WO97/03210); and
- iii. Claim 25 was rejected under 35 U.S.C. 103(a) over Zabeau and Little in view of Muller.

Applicant respectfully traverses these rejections. The new claims herein are introduced to expedite prosecution, and Applicant respectfully asserts the outstanding rejections are inapplicable to the subject matter claimed herein.

Rejection for alleged obviousness over Zabeau and Little

Claims 12-22, 24, 26-32, 34-39 and 58-73 were rejected under 35 U.S.C. 103(a) over Zabeau (WO00/66771) in view of Little. The rejection respectfully is traversed and Applicant respectfully submits the rejection is inapplicable to the new claims.

Claims 74-114 are directed to methods for determining one or more sequence variations in a target nucleic acid, which comprise providing mass signals of fragments resulting from specific cleavage of a target nucleic acid and a reference nucleic acid and identifying differences in mass signals between target nucleic acid fragments and reference nucleic acid fragments. One or more compomer witnesses are generated for the different fragments identified, and a reduced set of candidate sequence variations corresponding to the compomer witnesses is produced. The one or more sequence variations in the target nucleic acid are determined from the candidate sequence variations.

Claims 115-123 are directed to methods for detecting one or more sequence variations in a target nucleic acid, which comprise providing a plurality of fragmentation patterns resulting from specific cleavage of a sample comprising a target nucleic acid by multiple cleavage reactions, and specific cleavage of a reference nucleic acid by the same cleavage reactions. Differences in mass signals then are identified between the plurality of fragmentation patterns of target nucleic acid fragments and reference nucleic acid fragments. From the different fragments identified, those that are consistent with a particular sequence variation in the target nucleic acid are selected and combined to obtain a spectrum of different fragments. From the spectrum of different fragments, one or more compomer witnesses corresponding to each of the different fragments are generated, and sequence variation candidates are prepared from the compomer witnesses. The candidate sequences are scored and the one or more sequence variations in the target nucleic acid are determined.

Claims 124-128 are directed to specific methods for detecting one or more sequence variations in a target nucleic acid, which comprise providing reference sequence s , a description of cleavage reaction conditions, whether modified nucleotides or amino acids are incorporated into all or part of the sequence, a list of signals corresponding to different fragments, and maximal sequence variation order k . A list of sequence variations that contain at most k insertions, deletions, and substitutions, and that have a different peak as a witness, are generated. Bounded compomers ($c[i,j], b[i,j]$) in $C.sub.k$ are computed and stored with the indices i,j based on the reference sequence s and the specific cleavage reaction. Compomers are identified for each different signal having a mass close to the signal mass by a sufficiently small mass difference, and the compomers are stored as compomer witnesses. Bounded compomers (c,b) in $C.sub.k$ are determined for each compomer witness c' , where $D(c',c,b)$ is less than or equal to k ; and sequence variations of s are outputted to a new reference sequence s' using at most k insertions, deletions, and substitutions for each bounded compomer (c,b) with indices i,j .

Claimed matter is *prima facie* obvious only when a combination of cited documents (1) teaches or suggests all of the claimed elements, (2) the person of ordinary skill in the art was motivated to modify the document(s) as suggested in the Office action, and (3) there was a reasonable expectation of success. See MPEP 2142, et seq. The United States

Supreme Court recently upheld this “teaching, suggestion, motivation” framework and cautioned it should not be applied in a “rigid” manner (*K.S.R. Int’l. Co. v. Teleflex, Inc.*, No. 04-1350 (U.S. April 30, 2007)). Here, (i) the cited documents, alone or in combination, fail to teach or suggest all of the claimed elements, and (ii) Little teaches away from the claimed methods.

As addressed above, the claimed methods in general are directed to deriving sequence variance information from mass signals. In particular, the claimed methods are directed to identifying differences in mass signals for fragments generated by specific cleavage, assigning compomer witnesses to the different mass signals, and determining sequence variation candidates from the compomer witnesses.

The Office stated in the action dated December 5, 2006 (page 10), that Zabeau does not teach or suggest the use of compomer witnesses. The Office, however, is of the view that Little teaches the use of compomer witnesses. Specifically, the Office is of the view that when Little measures the masses of primer extension products and from these masses determines a specific allele of apolipoprotein E is present, Little determines a compomer witness.

Applicant respectfully submits that Little does not teach or suggest the use of compomer witnesses to identify sequence variation candidates, as claimed herein. Little discusses methods for analyzing mass extension products. There are a finite number of mass extension products that can be produced from the reaction conditions, and from these sequences, Little calculates a theoretical mass (e.g., page 546, right column). The mass of each extension product is determined experimentally and then matched to the theoretical mass.

Little therefore does not generate compomer witnesses. When matching an experimental mass signal to a theoretical mass signal, Little automatically determines the sequence of an extension product without the generation of compomer witnesses, since the product sequences are known. Little never needed to generate compomer witnesses, i.e., the possible nucleotide composition(s) corresponding to a mass signal, because the nucleotide composition of each extension product was certain and known. Thus, Little does not teach or suggest compomer witness elements of the claimed methods.

Further, the approach in Little is opposite to the claimed processes. While Little determines mass signals from known sequence variances, the claimed methods determine sequence variances from mass signals. As the sequence variances are determined from compomer witnesses in the claimed methods, Little teaches away from using compomer witnesses to determine sequence variation candidates.

Because Little (i) does not teach or suggest the use of compomer witnesses to determine sequence variation candidates, and (ii) teaches away from using mass signals to derive sequence variance information via compomer witnesses, the claimed subject matter is not *prima facie* obvious. Applicant therefore respectfully requests withdrawal of the obviousness rejection.

Rejection for alleged obviousness over Zabeau, Little and McCarthy

Claims 23 and 33 were rejected under 35 U.S.C. 103(a) over Zabeau and Little in view of McCarthy (WO97/03210). The rejection respectfully is traversed and Applicant respectfully submits the rejection is inapplicable to the new claims. The Office states McCarthy discloses the use of DNA glycosylases. McCarthy, however, does not remedy the defects of Zabeau and Little, and the combination of the cited documents does not render the claimed subject matter *prima facie* obvious. Withdrawal of the rejection respectfully is requested.

Rejection for alleged obviousness over Zabeau, Little and Muller

Claim 25 was rejected under 35 U.S.C. 103(a) over Zabeau and Little in view of Muller. The rejection respectfully is traversed and Applicant respectfully submits the rejection is inapplicable to the new claims. The Office states Muller discloses analysis of epigenetic changes in a nucleic acid. Muller, however, does not remedy the defects of Zabeau and Little, and the combination of the cited documents does not render the claimed subject matter *prima facie* obvious. Withdrawal of the rejection respectfully is requested.

CONCLUSIONS

Applicant respectfully submits all pending claims will be in condition for allowance upon entry of the amendments herein. Applicant respectfully solicits a prompt notification to this effect, and the Examiner is encouraged to contact the undersigned representative (contact information below) to promptly resolve any remaining issues or questions.

In the unlikely event a fee calculation document or other pertinent document is separated from this submission and the Office determines that an extension and/or other relief is required, Applicant petitions for any required relief, including extensions of time, and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. **50-3473**.

Respectfully submitted,

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By: /Bruce Grant/
Bruce D. Grant
Reg. No. 47608
Grant Anderson LLP
Customer No. 47328
Telephone: (858) 623-3226